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Clinical paper

The effect of a face mask for respiratory support on breathing in preterm infants at birth

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Abstract

Objective: Applying a mask on the face for respiratory support could induce a trigeminocardiac reflex leading to apnoea and bradycardia. We have examined the effect of applying a face mask on breathing and heart rate in preterm infants at birth.

Methods: Resuscitation videos of infants ≤ 32 weeks gestation recorded from 2010 until 2018 at the Leiden University Medical Centre and the General University Hospital in Prague were reviewed. All infants received respiratory support via face mask. Breathing and heart rate were noted before and after application of the face mask and over the first 5 min.

Results: Recordings of 429 infants were included (median (IQR) gestational age of 28^{+6} (27^{+1}-30^{+4}) weeks). In 368/429 (86%) infants breathing was observed before application of the face mask and 197/368 (54%) of these infants stopped breathing following application of the face mask. Apnoea occurred at a median of 5 (3−17) seconds after application of the face mask with a duration of 28 (22−34) seconds of the first minute. In a logistic regression model, the occurrence of apnoea after face mask application was inversely associated with gestational age (OR = 1.424 (1.281−1.583), $p < 0.001$). Infants who stopped breathing had a significantly lower heart rate 82 (66−123) vs 134 (97−151) bpm, $p < 0.001$) and oxygen saturation (49% (33−59) vs 66% (50−82), $p < 0.001$) over the first minute after face mask application, compared to infants who continued breathing.

Conclusion: Applying a face mask for respiratory support affects breathing in a large proportion (54%) of preterm infants and this effect is gestational age dependent.

Keywords: Preterm infants, Breathing, Face mask, Trigeminocardiac reflex, Respiratory support

Introduction

Preterm infants often need respiratory support during the transition at birth. As 80% of extremely preterm infants show signs of breathing immediately after birth,[1] non-invasive ventilation via face mask is most commonly used. This is thought to allow infants to breathe spontaneously and contribute to their own pulmonary ventilation after birth, while still allowing the application of positive pressure ventilation (PPV) if the infant requires further respiratory support.

Abbreviations: CPAP, Continuous positive airway pressure; DR, Diving reflex; FiO2, Fraction of inspired oxygen; GA, Gestational age; HR, Heart rate; LUMC, Leiden University Medical Centre; PEEP, Positive end-expiratory pressure; PPV, Positive pressure ventilation; RFM, Respiratory function monitor; SI, Sustained inflation; SpO2, Pulse oxygen saturation; TCR, Trigeminocardiac reflex.

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During audits of neonatal stabilisation and resuscitation procedures, we frequently noticed that breathing of preterm infants was affected by application of the face mask immediately after birth. This could be a result of the trigeminocardiac reflex (TCR), which is highly prominent in newborns and infants.[2–4] Placing a face mask over the mouth and nose covers the area of the trigeminal nerve. Stimulation of the trigeminal nerve can provoke a TCR leading to sudden respiratory and hemodynamic changes such as breath-holding (apnoea), reduction of heart rate (HR) and changes in blood pressure. Stimulation of the V1 subdivision of the trigeminal nerve is associated with hypertension, whereas the V2 and V3 subdivisions are associated with normotension or even hypotension.[2]

The trigeminal reflex is often referred to as the diving reflex (DR), which explains the changes in breathing and HR caused by submersion of the face in water. However, this reflex is a peripheral sub-classification of the TCR covering the V1 subdivision of the trigeminal nerve e.g. forehead and nasal mucosa. The DR can be triggered by the application of cold water or cold air-flow to the face, but application of a face mask has the potential to activate all V1 to V3 subdivisions of the trigeminal nerve, provoking an even larger reflex. In this article we will, therefore, refer to the TCR.[2]

Previous studies[5–7] have investigated the TCR in term infants and have found that infants with a regular breathing pattern became slightly hypo-ventilated after applying a face mask.[5] Others reported that the application of a face mask, or the face mask rim alone, significantly reduced breathing rate and increased tidal volumes for at least 5 min.[6,7] This suggests that the change in breathing was mainly due to trigeminal stimulation and only partly due to the added dead space.

While most preterm infants at birth are supported by positive pressure given non-invasively via face mask, activation of the TCR has not been previously considered or investigated in this situation. However, anecdotally, caregivers acknowledge that respiratory activity decreases following application of a mask to the face of preterm infants. We hypothesized that the effect on breathing could even be greater in preterm infants than previously demonstrated in term infants.[5–7] The aim of this retrospective observational study was therefore to examine the effect of face mask application on breathing and HR in preterm infants.

Methods

A retrospective observational study was performed at the tertiary level perinatal centres of the Leiden University Medical Centre (LUMC), the Netherlands, and the General University Hospital in Prague, Czech Republic. All available resuscitation videos of preterm infants ≤ 32 weeks recorded at the LUMC from March 2014 until October 2018 and at the General University Hospital in Prague from January 2010 until October 2018 were analysed. Recordings were included if (1) infants received respiratory support via face mask and (2) video recordings could be assessed on breathing before application of the face mask. Recordings were excluded if (1) infants on the recordings were unidentifiable, (2) the type of interface changed or (3) chest compressions were necessary in the first 5 min after applying the face mask.

Study protocols

At the LUMC, a face mask was used that was the appropriate size for the infant's weight (Neonatal Resuscitation Mask, Fisher & Paykel Healthcare Ltd, Auckland, New Zealand). Video and physiological measurements, such as HR, pulse oxygen saturation (SpO2), fraction of inspired oxygen (FiO2), and flow were collected by a respiratory function monitor (RFM) (Advanced Life Diagnostics, Weener, Germany) and the Polybench physiological software (Applied Biosignals, Weener, Germany), which has been previously described in detail.[8,9]

At the General University Hospital in Prague, a round silicone face mask (Laerdal Medical, Stavanger Norway) was used for respiratory support at birth. Video and physiological measurements, such as HR and SpO2 were monitored via the Masimo pulse oximeter (Masimo Radical, Masimo Corporation, Irvine, California, USA) and software TRAL (SPM-Seevice, Zelenograd, Russia) was used to evaluate all delivery room interventions as well as FiO2 settings. A RFM was not available.

In both centres were the gases heated and humidified. The Masimo pulse oximeter sensor was placed around the infants' wrist or hand as soon as possible after the infant was placed on the resuscitation table in all infants.

Study outcomes

The following patient characteristics were collected: gestational age (GA), birth weight, gender, Apgar score at 1 and 5 min, umbilical cord blood pH, mode of delivery, antenatal corticosteroids, placental transfusion and use of general anaesthetics. Placental transfusion was defined as cord milking or delayed cord clamping after 1 min.

Recordings were reviewed, at normal speed and half speed, and documented in a case report form. All the recordings were reviewed by one researcher (KK) and in case of doubt consensus was reached with the help of a second researcher (TL/TM). Breathing before application of the face mask was identified when chest excursions, crying and/or vivid spontaneous movements of the extremities were visible on the video in the time before the face mask was applied. Breathing after application of the face mask was identified when chest excursions were visible in 10–60 s after application of the face mask or until the start of PPV. If chest excursions were only visible during sustained inflation (SI), this was classified as 'not breathing'. Whenever available, the RFM was used to verify breathing after application of the face mask. Infants were classified as 'stopped breathing' when no breaths were visible for at least 20 s, ≤3 breaths were observed in the observation period or breaths were only visible during SI on the RFM.

Other interventions noted were SI, PPV, tactile stimulation, suctioning and intubation in the first five minutes after face mask application. Furthermore, HR, SpO2 and FiO2 before application of the face mask and 10 s, 30 s, 1 min and 5 min after application of the face mask were collected. If a flow sensor was used, positive end-expiratory pressure (PEEP) after application of the face mask was documented.

Ethics

The local institutional Research Ethics Committee of the General University Hospital in Prague and the LUMC approved the study protocol and issued a statement of no objection for performing this study.

Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics version 23 (IBM Software, Chicago, Illinois, USA, 2016) except the mixed models, which were analysed with R, version 3.5.0. Categorical data was analysed using a Chi-square test and presented as n (%). Continuous variables were tested for normality and were analysed and presented using the Mann-Whitney test median (IQR) or two-tailed t-test mean ± SD. A logistic regression was used to predict the effect of gestational age, gender and general anaesthesia, previously described as possible influencers of the TCR,[3,6,10–15] on the likelihood that participants keep breathing after application of a face mask. A mixed model was performed to evaluate HR and SpO2 in the first 5 min after application of a face mask using package *lme4* in R. A p value <0.05 was considered statistically significant.

Results

Recordings of 429 infants were included with a median (IQR) GA of 28^{+6} (27^{+1}-30^{+4}) weeks (Fig. 1,Table 1). In 368/429 (86%) infants, breathing was observed when the infant was placed on the resuscitation table. Of the 368 infants initially breathing, 197 infants (197/368; 54%) stopped breathing and 171 infants (171/368; 46%) continued breathing after application of the face mask (Table 2). Apnoea occurred at a median of 5 (3–17) seconds after applying the face mask and persisted for 28 (22–34) seconds of the first minute (Table 3). Of the infants <28 week, 125/153 (82%) were initially breathing of which 96/125 (77%) stopped breathing after face mask application.

Infants who stopped breathing after application of the face mask received PPV more often (79% vs 16%, $p < 0.001$) and sooner (70 (30–114) vs 152 (118–185) sec, $p < 0.001$) than the infants who continued breathing. SI was more frequently given to infants that stopped breathing (77% vs 29%, $p < 0.001$) and during the SI, 72/151 (48%) spontaneous breaths could be identified but remained apnoeic thereafter. Infants who stopped breathing received more frequent tactile stimulation (91% vs 79%, $p = 0.001$), suctioning (27% vs 7%, $p < 0.001$) and intubation in the delivery room (8% vs 1%, $p = 0.001$) (Table 3).

RFM recordings verified our observations in 248/368 (67%) cases. In 45/368 (12%) cases were RFM recordings difficult to read due to 100% leak, artefacts or movements of the infant and in 75/368 (20%) cases were no RFM measurements available. There was no difference in PEEP levels between the infants who stopped and continued breathing (4.9 ± 1.0 vs 4.8 ± 0.9 cmH2O, $p = 0.55$) (Table 3).

Infants who stopped breathing had a significantly lower HR and SpO2 in the first minute after face mask application (median heart rate (82 (66–123) vs 134 (97–151) bpm, $p < 0.001$) and median saturation (49% (33–59) vs 66% (50–82), $p < 0.001$)), without differences in

Table 1 – Characteristics of the patients.

Patients' characteristics	All infants N = 429
Gestational age in weeks, median (IQR)	28^{+6} (27^{+1} – 30^{+4})
Birth weight in grams, mean ± SD	1176 ± 377
Males, n (%)	229 (53)
Antenatal corticosteroids, n (%)	226 (53)
Caesarean delivery, n (%)	257 (60)
General anaesthesia, n (%)	52 (12)
Placental transfusion, n (%)	104 (59)[a]
Apgar score 1 min, median (IQR)	6 (3–7)
Apgar score 5 min, median (IQR)	8 (7–9)
Umbilical cord blood pH, mean ± SD	7.27 ± 0.12[b]

[a] 252 (59%) missing variables.
[b] 152 (35%) missing variables.

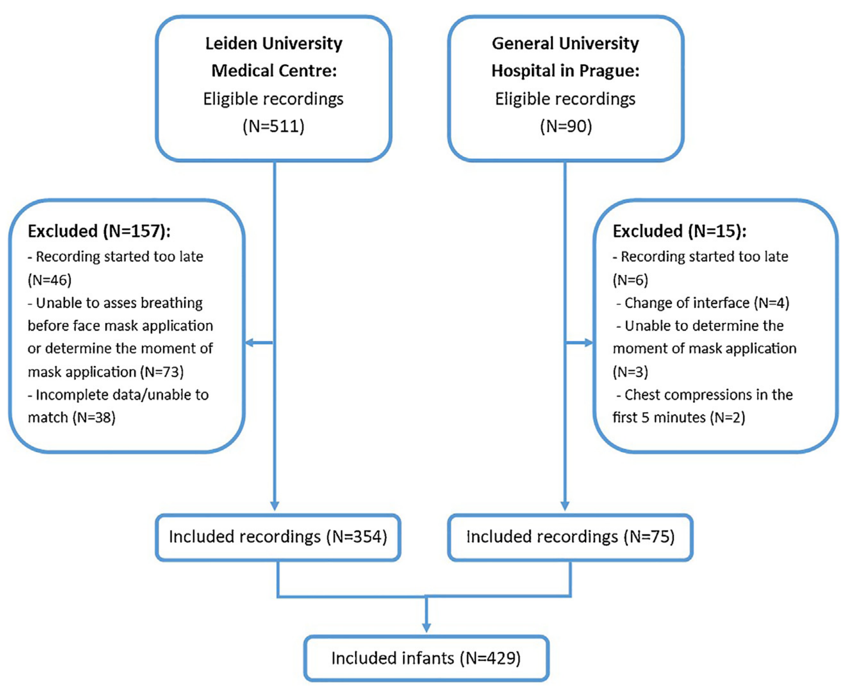


Fig. 1 – Study population. The LUMC and the General University Hospital in Prague stored 602 recordings of infants ≤ 32 weeks of gestation. Recordings were assessed for eligibility and excluded if we were unable to asses breathing before application of the face mask, if infants on the recording were unidentifiable, if the type of interface changed or chest compressions were necessary in the first 5 min after applying the face mask.

Table 2 – Breathing before and after face mask application.

Outcome	Signs of breathing before face mask (n = 368)	No signs of breathing before face mask (n = 61)	p-Value
Thorax excursions after face mask, n (%)			<0.001*
• Visible (continued breathing)	171 (46)	0 (0)	
• Not visible (stopped breathing[a])	197 (54)	61 (100)	
PPV is given, n (%)	183 (50)	57 (93)	<0.001*

PPV – positive pressure ventilation.
* Chi-square test.
[a] stopped breathing includes also infants with only visible thorax excursions during SI.

Table 3 – Delivery room outcomes and RFM data of infants who were initially breathing.

Outcome	Stopped breathing (n = 197)	Continued breathing (n = 171)	p-value
PPV is given, n (%)	156 (79)	27 (16)	<0.001*
Time until start PPV (sec), median (IQR)	70 (30-114)	152 (118-185)	<0.001**
SI is given, n (%)	151 (77)	49 (29)	<0.001*
Only thorax excursions during SI, n (%)	72 (48)		
Tactile stimulation, n (%)	179 (91)	135 (79)	0.001*
Suction, n (%)	54 (27)	12 (7)	<0.001*
Intubation rate, n (%)	16 (8)	1 (1)	<0.001*
RFM recordings, n (%)	147 (75)[a]	146 (85)[d]	
Observations verified, n (%)	106 (100)[c]	142 (100)[e]	
Time until apnoea (sec), median (IQR)	5 (3-17)[b]		
Duration apnoea (sec), median (IQR)	28 (22-34)[b]		
PEEP, mean ± SD	4.9 ± 1.0[a]	4.8 ± 0.9[d]	0.55***

PPV – positive pressure ventilation; SI – sustained inflation; PEEP – positive end-expiratory pressure.
[a] 50 (25%) missing.
[b] 153 (78%) missing.
[c] 41 (21%) difficult to read due to 100% leak or artefacts.
[d] 25 (15%) missing.
[e] 4 (2%) difficult to read due to 100% leak, artefacts or movements.
* Chi square.

** Independent samples Mann–Whitney U test.

*** Independent t-test.

FiO2. FiO2 given at 5 min was significantly higher in infants who stopped breathing (51% (31–97) vs 31% (24–50), $p < 0.001$), without differences in HR and SpO2 between the two groups (Fig. 2).

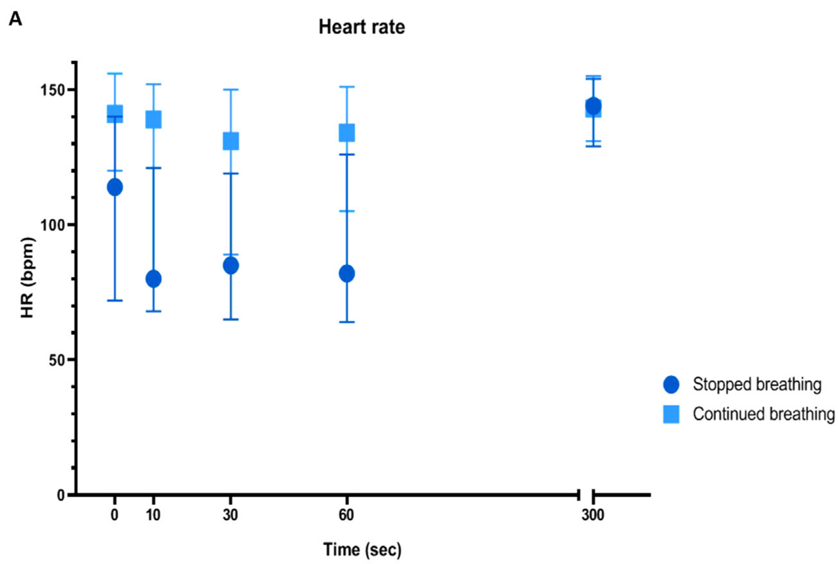
Logistic regression was used to predict the effect of GA, gender and general anaesthesia on the likelihood that participants keep breathing after application of the face mask and was statistically significant ($\chi2(3) = 58.936$; $p < 0.05$). The model explained 17.4% (Nagelkerke R^2) of the variance in the effect of the application of the face mask on breathing and correctly classified in 65.3% of the infants. Increasing age was associated with an increased likelihood to keep breathing after application of the face mask (OR = 1.424 (1.281–1.583), $p < 0.001$) (Table 4).

Discussion

In this large retrospective cohort study, we observed that a large proportion of preterm infants stopped breathing and received PPV after a face mask was applied. The occurrence of apnoea after face mask application was inversely associated with GA. These findings suggest that the face mask could trigger the TCR thereby compromising the capacity of infants to breathe and contribute to their own pulmonary ventilation, increasing the necessity of applying PPV. In view of its propensity to stimulate this reflex, a face mask might not be the best interface for applying respiratory support in preterm infants at birth. It is currently unknown whether other interfaces, such as prongs, might be a good alternative for avoiding the TCR.

This is the first study to review the effect of a face mask on breathing in preterm infants at birth. The changes in breathing after face mask application are consistent with previous findings in term infants that displayed a decrease in breathing rate after face mask application.[6,7] However, as only 24% of term infants had a reduction in breathing rate,[6] whereas we observed a larger proportion of preterm infants (54%) that were affected, we considered that the inhibitory effect of face mask application was GA dependent. Indeed, we found a highly significant inverse relationship between GA and breathing rate in our cohort. This is consistent with the findings of a previous study, which triggered the TCR using an airstream flow.[13]

While previous studies have reported that trigeminal nerve stimulation induces a reflex bradycardia[11–13,16–19], we did not observe this in our study. However, HR measurements before face mask application were only available in 12/197 (6%) infants who



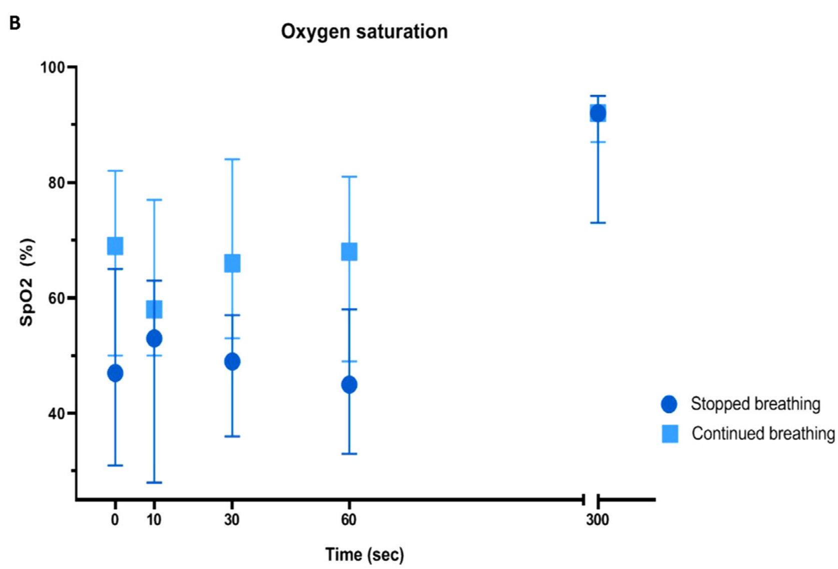


Fig. 2 – (A) Heart rate. Data of infants who were initially breathing, is presented as median (IQR). Time = 0 represent the heart rate before the face mask was applied. Data of infants who stopped or continued breathing is calculated based on n = 12 and n = 16 at t = 0, respectively, and n = 37 and n = 35 at t = 10. All other presented data is based on n > 100. (B) Oxygen saturation. Data of infants who were initially breathing, is presented as median (IQR). Time=0 represent the saturation before the face mask was applied. Data of infants who stopped or continued breathing is calculated based on n = 14 and n = 19 at t = 0, respectively, and n = 48 and n = 45 at t = 10. All other presented data is based on n > 100.

stopped breathing. Furthermore, the presence of breathing does not necessarily mean that the lung has aerated and pulmonary blood flow has increased. As such, many of these infants may have been bradycardic/mildly bradycardic due to a loss in cardiac output caused by umbilical cord clamping prior to increasing pulmonary blood flow, which masked the effect of TCR activation.[20] Nevertheless, HR was significantly lower in the first minute after application of the face mask in infants who stopped breathing. While this suggests that HR is affected by application of the face mask in the infants in which apnoea occurs, it is also possible that these infants were slightly more hypoxic upon application of the face mask. This raises the interesting question as to whether TCR application is additive to the inhibitory effect of hypoxia on breathing activity, which is a known potent inhibitor of breathing in the foetus and newborn.[21]

In addition to activation of mechanoreceptors in response to application of the face mask, other pathways may influence the TCR. An airstream (flow 15 L/min, temp 25 °C) delivered into nostrils at 1 cm distanced from the infants' face can stimulate the nasal mucosa and skin and trigger the TCR[13] leading to a reduction in HR and breathing rate in preterm infants. Other factors that induce cardio- respiratory

Table 4 – Logistic regression analyse of infants who were initially breathing.

	Odds ratio	95% CI odds ratio lower upper		p-Value
Gestational age in weeks	1.424	1.281	1.583	<0.001
Males	0.709	0.468	1.075	0.11
General anaesthesia	0.587	0.293	1.175	0.13

Note: $\chi 2(3) = 58.936$, $p < 0.05$, R^2 (Nagelkerke):0.174, correctly classified in 65.3% of the infants.

responses include: ocular pressure,[16] flow or water temperature,[12] antenatal nicotine exposure,[3] emotional factors,[10,12] anaesthetics[15] and maternal medication e.g. beta-adrenergic agonists.[14] As stimulation of the nasal mucosa by air[13] and application of a face mask rim[6,7] both affect breathing and HR, the reflex is unlikely to be exclusively a DR and may require a threshold to be reached before the TRC is triggered.[6] As such, the amount pressure exerted in squeezing the mask to reduce mask leak, may determine whether a TCR is induced, but it was not possible to review this retrospectively in the video recordings.

TCR could be avoided by using a nasal tube and thus decrease the effect of the TCR. Yet, these findings could not be confirmed by van Vonderen et al.[22] when comparing the use of a single nasal tube with a face mask as interface during stabilisation at birth. Lower tidal volume due to high leak and more often obstruction was observed when a single nasal tube was used, but breathing rate and HR were not significantly different between the two groups during the first 5 min after birth. A large (n = 250) randomised controlled trial, CORSAD, using nasal prongs for the neonatal stabilisation is currently ongoing.[23]

In accordance with previous studies,[24,25] in a large proportion of the infants who stopped breathing spontaneous breaths were observed during SI. The mechanism of breathing during SI could counteract bradycardia. An experimental model with dogs[16] investigating the oculocardiac reflex, which is part of the TCR, suggested that inflation of the lung could interrupt the TRC and reduce bradycardia. Despite inflation of the lung overcoming bradycardia, the HR decreases within a few seconds as the inspiratory effort concludes, even when lung inflation was maintained. This decrease in HR was caused by silencing of the phrenic nerve activity, presumably by provoking the Hering-Breuer inflation reflex through excitation of pulmonary afferents by inflation of the lungs.

The study is limited by its retrospective and observational design. Analyses of the recordings are dependent of the camera position hence visibility of the infants' thorax and visual assessment of thorax excursions have proven to be inaccurate.[26] When infants were vigorously moving, the assessment of breathing before application of the face mask was more difficult and made it likely that infants were breathing. Assessment of breathing after application of the face mask was more difficult as the mask and, occasionally, the plastic wrap obstructed the view. However, assessing breathing before applying a face mask or without a RFM is only possible through live assessment in the resuscitation room or analysing retrospective recordings. The fact that only one researcher reviewed the recordings limits the study. However, in 248/368 (67%) infants we could verify our observations with the RFM recordings, which can be considered golden standard, and our observations were consistent with the RFM in 100% of the cases. In the remaining cases no RFM measurements were available (75/368) or RFM was available but difficult to read due 100% leak, artefacts or movements of the infant (45/368). However, since in 2/3 of the cohort RFM was available for comparison and we reached 100% consistency, observing breathing on video was very accurate. Objective physiological parameters e.g. HR and SpO2 confirmed the observations as well, however they might underestimate the actual effect. Unstable infants likely receive respiratory support earlier and have less peripheral perfusion, reducing the chance to receive adequate measurements before applying the face mask. Furthermore, it is difficult to prove causality between face mask application and the reduction in breathing/HR, as result of the study design and due to the medical necessity of the face mask during standard medical care. Due diligence is needed when evaluating whether support is needed or not, since it might not be harmless. It is possible that infants in our group received support while not needed.

The decision to start PPV, SI, suction, tactile stimulation, intubation, and continuous positive airway pressure (CPAP) levels are described in guidelines but determined by observations and interpretations of the clinicians. The use of RFM increased the awareness that most preterm infants breathe spontaneously and more infants received CPAP as initial support, which could have influenced the presence of TCR.

Conclusions

In conclusion, applying a face mask for respiratory support at birth might compromise breathing in preterm infants by stimulating the trigeminal nerve and provoking the TCR. Clinicians should be aware that applying a face mask might compromise the breathing they intended to support, therefore due diligence is needed when evaluating whether respiratory support is needed or not. Further studies are warranted to confirm this finding since many preterm infants could be affected by the reflex. Also, we need to investigate whether avoiding the sensitive area around the mouth by using alternative interfaces e.g. nasal prongs would decrease the risk of inducing TCR.

Conflicts of interest

None.

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